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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; published online May 5. http://dx.doi.org/10.1016/S1473-3099(17)30243-8.

Appendix

Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infectious Diseases.* 2017.

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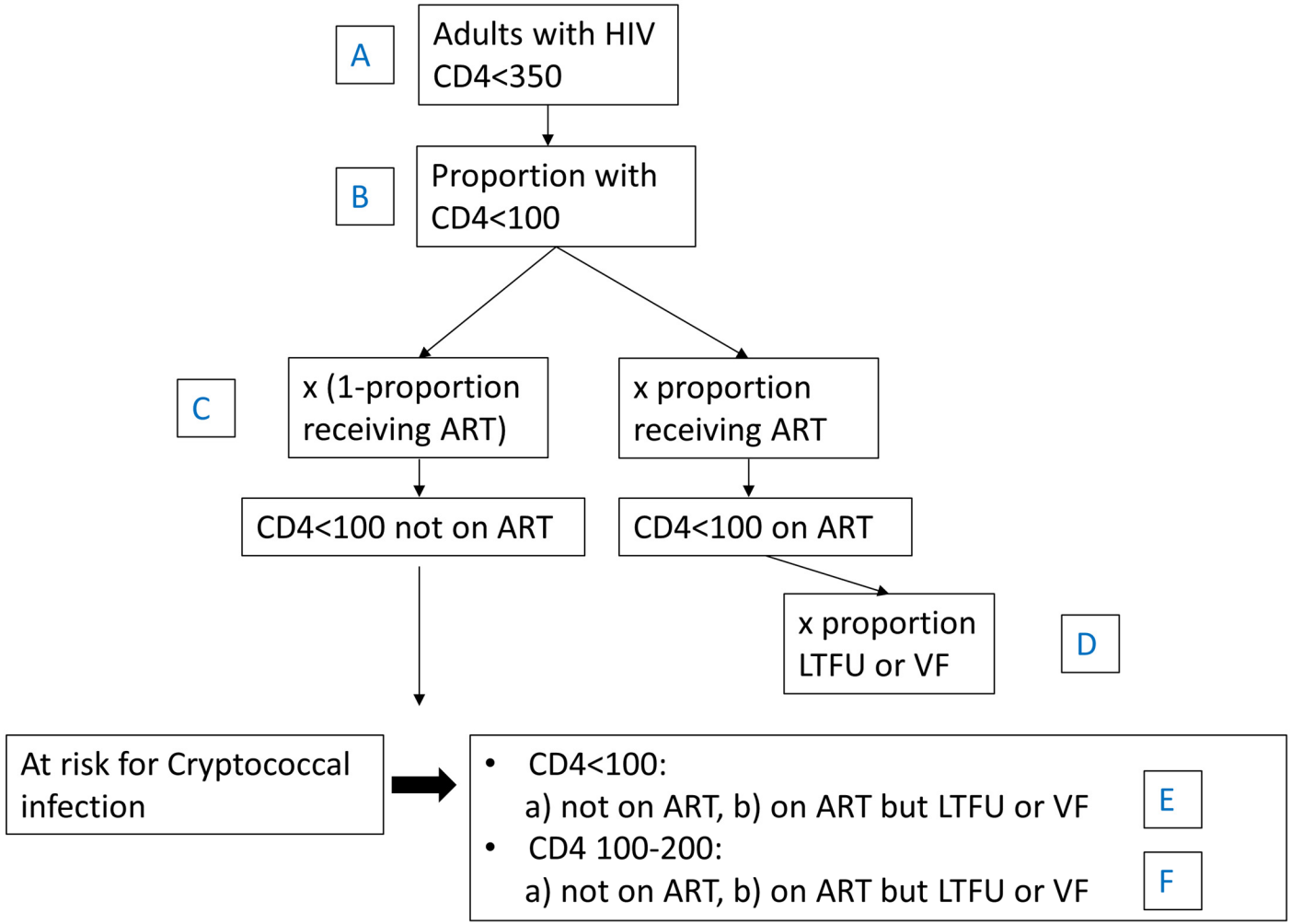
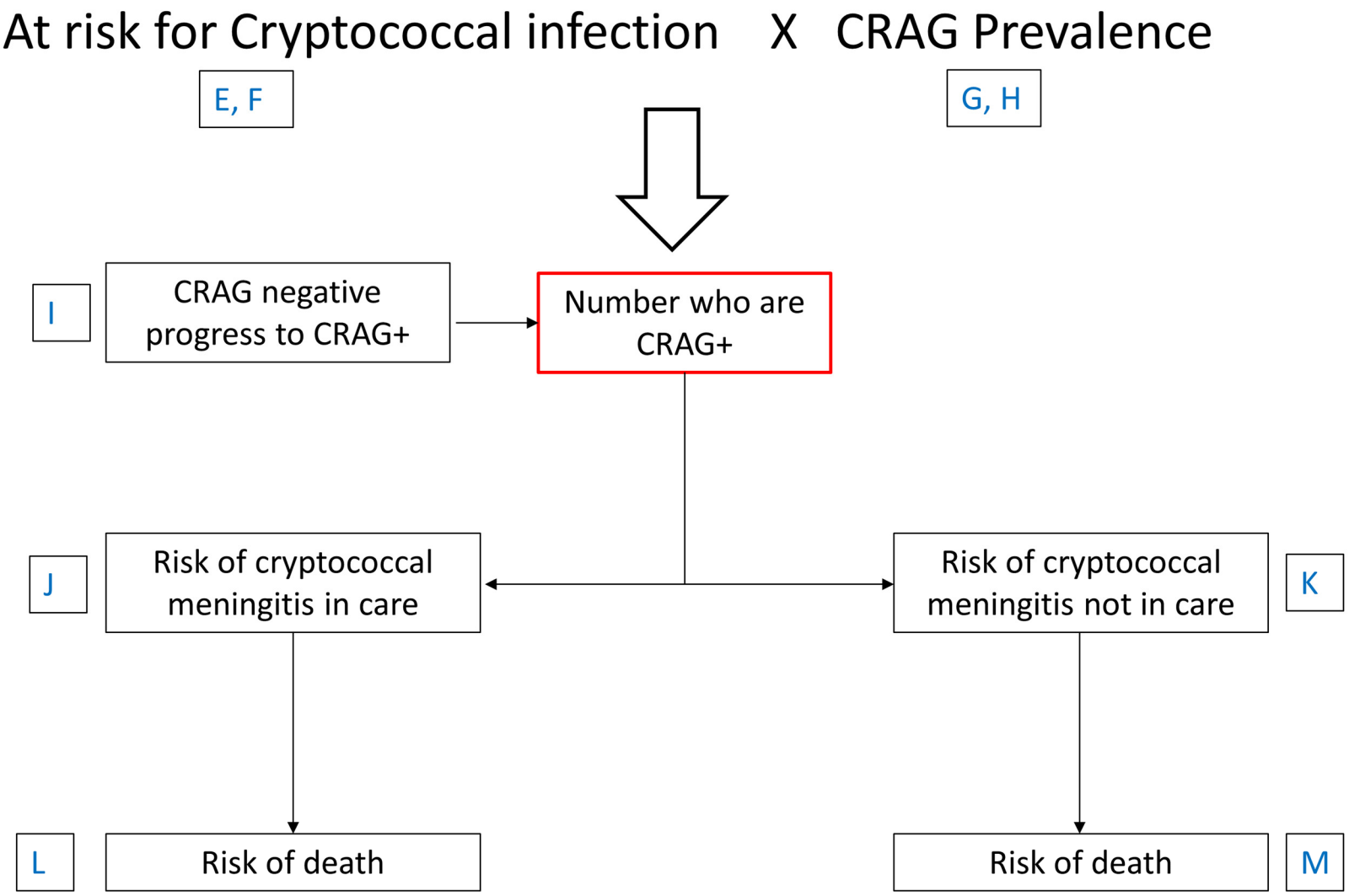
Supplemental Figure 1: Methodology of calculations of those at risk for cryptococcal infection, CRAG+, number who develop cryptococcal meningitis, and number who die of cryptococcal meningitis.



Notes: LTFU = Lost to follow up; VF = viral failure; LMICs = low and middle-income countries; HICs = high-income countries.
CD4 100-200 calculated as above though percentage of CD4<350 is 27.5% in LMICs, and 31.5% in HICs (refer to Table 1)
Boxed letters correspond to Table 1


At risk for Cryptococcal infection
X
CRAG Prevalence
E, F
G, H
I
CRAG negative progress to CRAG+
Number who are CRAG+
J
Risk of cryptococcal meningitis in care
Risk of cryptococcal meningitis not in care
K
L
Risk of death
Risk of death
M

Supplemental Methods

Global Burden of HIV Infection

Details regarding the assumptions behind the UNAIDS uncertainty bounds are published.[1] Where possible we used UNAIDS and WHO reports and multinational studies, as these estimates were less biased than single-center country-specific research publications. However, for many high-income countries in Europe and North America no estimates were made by UNAIDS or WHO of adults eligible for ART, receiving ART, or percent coverage. As available, UNAIDS Country Progress reports were used for Canada and China. U.S. HIV statistics were taken from CDC reports.[2] Regional estimates for Africa, Asia and Pacific, Caribbean, Latin America, and Western Pacific were simply the sum of each country's UNAIDS estimate. Notably, Japan, Korea, and New Zealand were not included in the Asian estimate, due to lack of accurate data. UNAIDS regional estimates were used for Europe, Eastern Mediterranean and North African region given that many country-specific estimates were unavailable.

CRAG Prevalence

For countries with available data, CRAG prevalence amongst persons with a CD4<100 cells/μL was used for that specific country along with the associated 95%CI. If the source cited CRAG prevalence for those with CD4>100 cells/μL, raw numbers were analyzed as possible to calculate CRAG prevalence and confidence interval for CD4<100 cells/μL. If raw numbers were not available, we still included the study in this analysis. If more than one study existed for a country, a weighted average with 95%CI was calculated, based on study size. For countries without specific published data, a weighted mean of the CRAG prevalence for the region with 95%CI was used as an estimate. As there were no studies published in the Caribbean, a weighted average of CRAG prevalence from Latin America was used. All literature cited refers to *Cryptococcus neoformans*, not *gattii* infection.

There is a small risk of cryptococcal disease amongst those with CD4 >100 cells/μL.[3-5] We estimated the number with a CD4 between 100-200 cells/μL as 27.5% (24% to 31%) of those with CD4<350 cells/μL in LMICs. In HICs we estimated 31.5% (29% to 34%) of those with a CD4<350cells/μL had a CD4 between 100 and 200 cells/μL.[6,7] In persons with CD4 100-200 cells/μL, we estimated a CRAG prevalence of one fourth of the prevalence amongst those with a CD4<100 cells/μL, based on a weighted average of CRAG prevalence in those with CD4>100 cells/μL compared with CD4<100 cells/μL.[3-5,8-18]

CRAG-positive persons who develop Cryptococcal Meningitis

Estimates of the number of CRAG-positive adults who go on to develop symptomatic cryptococcal meningitis were from published cohort studies,[3,4,10,19,20] where 33% (95%CI: 25% to 41%) of CRAG-

positive persons had prevalent disease at time of screening or developed *known* cryptococcal meningitis after initiating ART. In those research cohorts, 60% (72/121) died (95%CI: 50% to 68%).[3,4,10,19,20] Notably, these research studies reported a short time from CRAG positivity to ART initiation (≤2 weeks), and all of them were performed in sub-Saharan Africa or Asia. In routine care, there is likely further delay in initiating ART, and thus increased disease progression to meningitis. However, ART-mediated immune recovery may unmask the initially subclinical disseminated cryptococcal infection resulting in non-meningitis disease presentations (e.g. sepsis, pneumonitis).[3,21] From these studies, we presumed that a significant proportion of those CRAG+ who died of unknown causes or were lost to follow up in these studies were in fact deaths related to cryptococcosis. Including those who died or were lost to follow up as presumed cryptococcosis, we estimated 70% (Range: 56% to 82%) of CRAG+ persons developed cryptococcal disease or died despite initiating ART, unless preemptively treated. Without ART or preemptive fluconazole therapy, we assumed 95% (Range: 90% to 100%) progression in all regions (consensus expert opinion of authors).[22,23]

Cryptococcal Meningitis Deaths

We used UNAIDS country-level data on ART access as the surrogate for the proportion with access to quality medical care. We estimated 1-year mortality in low-income countries (LICs) as 70% (95%CI: 59% to 81%) after cryptococcal meningitis for those in care and 100% for those not in care.[30, 47-52] Uncertainty ranges were calculated by pooling the data from each paper, and calculating the 95% confidence interval. Data from research clinical trials suggest 10-week mortality of 39% (95%CI: 36% to 42%), with additional ~15% mortality through 1-year.[9,24,25] Outside of research trials, we expected mortality to be higher.[22] Many in LICs lack an initial diagnosis, receive fluconazole monotherapy, and do not receive therapeutic lumbar punctures, thus 70% mortality may be optimistic.[9,25-32] All sub Saharan African countries were considered low-income countries for the purpose of this estimate. Despite South Africa and Botswana having a higher GDP than most other African nations, the rate of CRAG+ progression and mortality from cryptococcal meningitis in these countries is similar to those of low-income nations.

Uncertainty Analysis

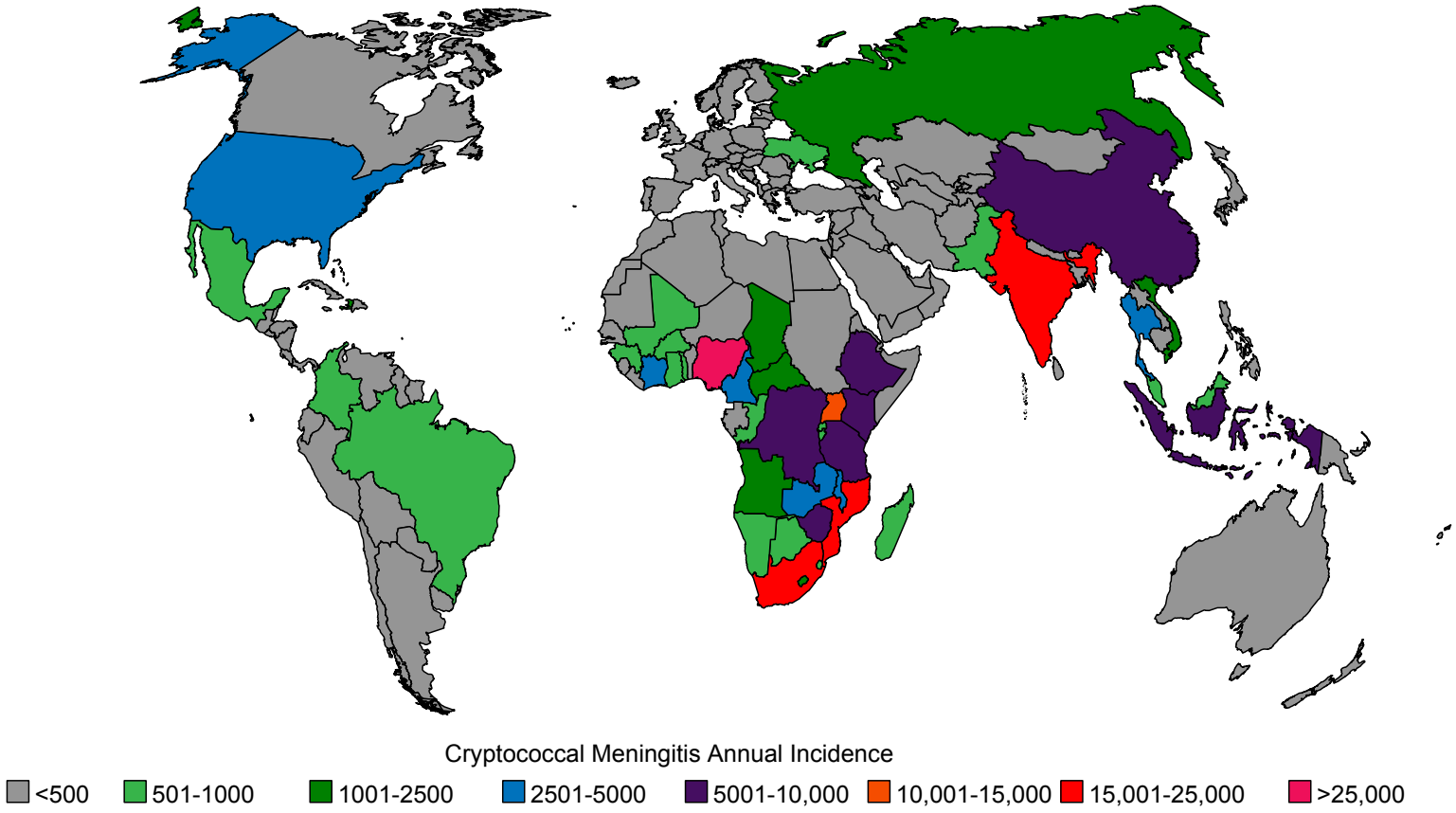
When data were lacking, we used expert opinion to define distributions, based on previously published estimates. Specifically, expert opinion of the authors was used to estimate progression from CRAG+ to cryptococcal meningitis for those not in care, as for those not in care there are no published estimates in the literature. Deaths from cryptococcal meningitis for those not in care were also estimated this way.

Supplemental Table 1: Estimation and Uncertainty Model Inputs

Model Input	Data Source(s)	Distribution	Parameters
Adults living with HIV	UNAIDS 2013 estimate: 31.8 million		Published low, high values: 30.1 million, 33.7 million
Adults with CD4<350 cells/ μL	UNAIDS 2013 estimate of those eligible for ART (i.e. CD4<350 cells/ μL): 19.5 million		Low, high values: 18.5 million, 20.7 million – from UNAIDS 2016 range
Adults receiving ART	UNAIDS 2013 estimate 11.3 million		Published low, high values: 10.4 million, 12.7 million
New initiation of ART	UNAIDS 2013, 2014 of Receipt of ART minus LTFU		Low, high values: 1.8 million, 2.8 million (80% and 120% of estimate)
CD4<100 cells/μL (LMICs)	22.5% of those with CD4<350 cells/ μL [6,7,33-35]	Beta	Low, high values: 19%, 26%;
CD4<100 cells/ μL (HICs)	18.5% of those with CD4<350 cells/ μL [6,7,33-35]	Beta	Low, high values: 16% to 21%;
CD4 100 to 200 cells/ μL (LMICs)	27.5% of those with CD4<350 cells/ μL [6,7,33-35]	Beta	Low, high values: 24% to 31%;
CD4 100 to 200 cells/ μL (HICs)	31.5% of those with CD4<350 cells/ μL [6,7,33-35]	Beta	Low, high values: 29% to 34%;
Virologic failure (within first year of ART)	16% of those on ART	Beta	Low, high values: 12% to 20%;
Virologic failure (after 1 year on ART)	5.33% of those on ART	Beta	Low, high values: 4.0% to 6.6%;
CD4 100 to 200 cells/ μL not on ART, LTFU, or virologic failure	25% of those with CD4<100 not on ART, or LTFU, or with virologic failure [3,12]	Beta	N/A
CRAG prevalence for countries without primary data	Regional weighted average	Normal	Computed 95% CI
CRAG+ who develop meningitis			
-- In care without preemptive treatment	70% [3,4,10,19,20]	Beta	Low value, high value: 56%, 84%;
-- Not in care	95% [3,4,10,19,20]	Beta	Low value, high value: 90%, 100%;
CRAG negative progression to CRAG+ without ART (LMICs)	5.1% annual incidence with 50% competing risk for starting ART or death	Beta	Low value, high value: 2.6%, 9.0%;
CRAG negative progression to CRAG+ without ART (HICs)	2.55% annual incidence with 50% competing risk for starting ART or death	Beta	Low value, high value: 0.1%, 1.0%;
1-year mortality from meningitis (LICs)	70% [9,25,28-32]	Beta	Low value, high value: 59%, 81%;
1-year mortality from meningitis (MICs)	40% [9,36-38]	Beta	Low value, high value: 34%, 46%;
1-year mortality from meningitis (North America)	20% [39,40]	Beta	Low value, high value: 12.5%, 27.5%;
1-year mortality from meningitis (Europe)	30% (including Ukraine, Russia)	Beta	Low value, high value: 25%, 35%;
Not in care (all regions)	1.5x higher [22]		N/A

LTFU =Lost to follow up; LIC = low income country; MIC = middle income country. References numbers as in the manuscript.

Supplemental Figure 2: Cryptococcal meningitis annual incidence. Annually, an estimated 223,100 (95% CI, 150,600 to 282,400) cryptococcal meningitis cases occur globally.



Supplemental Table 2: Cryptococcal Antigen Prevalence Rates (Source Data for Figure 1)

Year	*Author*	*Country*	*Setting*	*Overall prevalence*	*Numerator*	*Denominator*	*95%CI Lower*	*95%CI Higher*	*HIV severity*
1989	Desmet [41]	Dem. Rep. of the Congo	Newly diagnosed HIV+ patients	12.2%	55	450	9.3%	15.6%	Unknown
1992	Swinne [42]	Rwanda	Random HIV+ sera	4.2%	9	213	2.0%	7.9%	Unknown
1995	Negroni [43]	Argentina	Unknown	6.7%	13	193	3.6%	11.2%	193 CD4 <300
2003	Tassie [44]	Uganda (Mbarara)	Inpatient (n=144) and outpatient (n=53) HIV+	4.4%	8	182	1.9%	8.5%	Stage III or IV
2007	Liechty [45]	Uganda (Tororo)	HIV+ initiating ART	5.8%	22	377	3.7%	8.7%	CD4 <100
2007	Micol [46]	Cambodia	HIV+ seen at hospital associated ART programs	10.8%	32	295	7.5%	15.0%	CD4 <200
2009	Jarvis [19]	South Africa (Cape Town)	HIV+ initiating ART	6.7%	21	312	4.2%	10.1%	CD4 <100
2010	Meya [3]	Uganda (Kampala)	HIV+ initiating ART	8.8%	26	295	5.8%	12.6%	CD4 <100
2010	Pongsai [10]	Thailand (Bangkok)	HIV+, ART-naïve	12.9%	11	85	6.6%	22.0%	CD4 <100
2011	Parkes-Ratanshi [12]	Uganda (Masaka)	HIV+, ART-naïve adults	7.8%	59	757	6.0%	9.9%	CD4 <100
2011	Mamoojee [47]	Ghana	HIV+ initiating ART	2.0%	2	92	0.3%	7.6%	CD4 <100
2011	Kendi [48]	Kenya	HIV+ initiating ART	7.2%	66	920	5.6%	9.0%	CD4 ≤100
2012	Osazuwa [11]	Nigeria	HIV+ initiating ART	12.7%	19	150	7.8%	19.1%	CD4 <200
2012	Linares [49]	Peru (Lima)	HIV+, ART-naïve	3.6%	13	365	1.9%	6.0%	CD4 ≤100
2012	Kwan [13]	Thailand	HIV+ women initiating ART	11.0%	9	84	5.0%	19.4%	CD4 <100
2012	Bedell [50]	Malawi	HIV+ initiating ART	1.7%	8	469	0.7%	3.3%	All (median=129)

2013	Alemu [14]	Ethiopia (Addis)	HIV+, both ART-naïve and ART-experienced	11.2%	13	116	6.1%	18.4%	CD4 <100
2013	Patel [51]	U.K. (London)	Newly diagnosed HIV+ patients	5.0%	8	157	2.2%	9.8%	CD4 <100
2013	Meyer [48]	Kenya (multisite)	HIV+ initiating ART	9.1%	117	1286	7.6%	10.8%	CD4 ≤100
2013	Escandón [52]	Colombia	ART-naïve HIV+	7.1%	21	297	4.4%	10.6%	All
2013	Smith [53]	Vietnam (multisite)	HIV+ initiating ART	4.0%	9	226	1.8%	7.4%	CD4 <100
2013	Chukwuanukwu [54]	Nigeria	Pregnant HIV+	13.0%	21	160	8.3%	19.4%	All
2013	Rugemalila [15]	Tanzania (Moshi)	Outpatient HIV+ initiating ART or on ART<6 months	4.8%	6	124	1.8%	10.2%	CD4 <100
2013	Beyene [5]	Ethiopia (Oromia Region)	HIV+ initiating ART-naïve and defaulters	15.5%	16	103	9.1%	24.0%	All
2013	Costa[17]	Brazil (Para State)	HIV+ in 2 HIV clinics on ART	2.6%	11	418	1.3%	4.7%	All
2014	McKenney [55]	U.S. (multisite)	Stored sera of HIV+ both ART-naïve and ART-experienced	2.9%	54	1,872	2.2%	3.7%	CD4 <100
2014	Drain [56]	South Africa (Durban)	HIV+ initiating ART in 4 outpatient sites, urine LFA	8.7%	67	773	6.8%	10.9%	CD4 ≤100
2014	Ganiem [57]	Indonesia	Stored sera of HIV+ ART-naïve outpatients in 1 clinic using LFA	7.1%	58	810	5.5%	9.2%	CD4 <100
2014	Sawadogo [7]	Namiba	Prospective CD4	4.1%	21	516	2.5%	6.2%	CD4 <100
2014	MSF [58]	Dem. Rep. of the Congo	HIV Outpatient Clinic	15.2%	93	613	12.4%	18.3%	CD4 <100
2014	MSF [58]	Guinea	HIV Outpatient Clinic	4.9%	4	82	1.3%	12.0%	CD4 <100
2014	MSF [58]	Mozambique	HIV Tertiary Referral Clinic	6.6%	11	166	3.4%	11.5%	CD4 <100

2014	MSF [58]	Lesotho	HIV Outpatient Clinic	5.4%	3	56	1.1%	14.9%	CD4 <100
2014	MSF [58]	Kenya (Kibera)	HIV Outpatient Clinic	12.8%	17	133	7.6%	19.7%	CD4 <100
2014	MSF [58]	Zimbabwe (Gutu, Buhera)	HIV Outpatient Clinic	7.1%	32	448	4.9%	9.9%	CD4 <100
2014	Magambo [59]	Tanzania (Mwanza)	HIV Outpatient Clinic	8.2%	6	73	3.1%	17.0%	CD4 <100
2015	Letang [4]	Tanzania (Ifakara)	Stored plasma samples of HIV+ ART-naïve patients	4.3%	24	556	2.8%	6.4%	CD4 <100
2015	Govender [60]	South Africa (Gauteng)	HIV+ patients of 26 health facilities	4.0%	60	1494	3.1%	5.1%	CD4 <100
2015	Chipungu [55]	Malawi	Outpatient CD4<100	3.5%	2	57	0.4%	12.1%	CD4 <100
2015	Mfinanga [61]	Tanzania, Zambia	Outpatient CD4<100	4.6%	33	717	3.2%	6.4%	CD4 <100
2015	Pac [62]	Uganda	Outpatient CD4<100	6.8%	12	177	3.6%	11.5%	CD4<100
2016	Morawski [63]	Uganda (Multisite)	Outpatient CD4<100	8.7%	162	1860	7.5%	10.1%	CD4 <100
2016	Longley [64]	South Africa	Outpatient CD4<100	4.3%	28	645	2.9%	6.2%	CD4 <100
2016	Oladele [65]	Nigeria	Outpatient CD4<250	9.8%	6	61	4%	20%	CD4 <100
2016	Ezeanolue [66]	Nigeria	Outpatients CD4<100	3.7%	52	1399	2.8%	4.8%	CD4<100
2016	Vallabhaneni [67]	South Africa	Outpatients CD4<100	2.1%	24	1170	1.3%	3.0%	CD4<100
2016	Ogouyemiz [68]	Benin	Outpatients CD4<100	3.9%	6	154	1.0%	8.0%	CD4<200
2017	Kadam D [69]	India	Outpatient CD4<100	6.1%	11	180	3.1%	10.7%	CD4 <100
Total			**Outpatients Only**	**6.4%**	**1365**	**21487**	**6.0%**	**6.7%**	
Total			**Outpatients LMIC**	**6.7%**	**1303**	**19458**	**6.3%**	**7.1%**	

Studies of Primarily Hospitalized Populations not included in Figure 1.

Year	*Author*	*Country*	*Setting*	*Overall prevalence*	*Numerator*	*Denominator*	*95%CI Lower*	*95%CI Higher*	*HIV severity*
1997	Grant [70]	Ivory Coast	Inpatient HIV+	2.5%	5	199	0.8%	5.8%	All
2008	Oumar [71]	Mali	Inpatient HIV+ patients in 1 ID unit hospital	3.1%	4	115	1.0%	8.7%	All
2011	Wajanga [72]	Tanzania	HIV+ inpatients	5.1%	17	333	3.0%	8.0%	All
2011	Apetse [73]	Togo	HIV+ inpatient 22 health sites India Ink, CrAg latex agglutination	2.9%	21	714	1.8%	4.5%	All
2012	Oyella [74]	Uganda	HIV+ inpatients (97%) and outpatients (3%)	19%	70	367	15.2%	23.5%	CD4 < 100
2012	Dzoyem [75]	Cameroon	Inpatient HIV+						
2013	Luma[76]	Cameroon	HIV+ patients	11.2%	75	672	8.9%	13.8%	All
2014	Okome-Nkoumou [77]	Gabon	HIV+ ART-naïve patients in 1 ID unit	0.44%	2	458	0.1%	1.6%	All
2015	Katchanov [78]	Germany	Hospital Admissions CD4<100	1.6%	28	1723	1.1%	2.3%	CD4 <100
2015	Frola [79]	Peru (Lima)	CD4<100 hospital	8.8%	10	114	4.3%	15.5%	CD4 <100
2016	Vidal [80]	Brazil	Inpatients CD4<200	3.1%	5	163	1.0%	7.0%	CD4 <200

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